REMARKS

A. REQUEST FOR RECONSIDERATION

Applicants have carefully considered the matters raised by the Examiner in the outstanding Office Action dated October 28, 2008, but remain of the opinion that patentable subject matter is present. Applicants respectfully request reconsideration of the Examiner's position based on the four Terminal Disclaimers and the following remarks.

B. STATUS OF THE CLAIMS

Claims 1, 3-21, 23-38, 40-64, 69-74, 78-83, 87-89, 93 and 99-146 are presented for further prosecution.

No amendments have been made herein.

C. PRIOR ART REJECTIONS

The Examiner has made the following four rejections:

(1) Claims 1, 3-21, 23-38, 40-64, 69-74, 78-83, 87-89, 99-112, 117-119 and 122-128 are unpatentable over Hochrainer et al. (U.S. 6,150,418) in view of Carling et al. (U.S. 5,674,860) and PDR;

(2) Claim 93 is unpatentable over Hochrainer in view of Carling and PDR, and further in view of PDR, pages 482, 535, 537 and 2828;

(3) Claims 113-116 and 120-121 are unpatentable over Hochrainer in view of Carling and PDR, and further in view of Hardman et al. (Goodman Gilman's *The Pharmacological Basis of Therapeutics*, 1996, page 665) or Leckie et al. (*Novel Therapy of COPD*, abstract, Jan 2000); and

(4) Claims 129-146 are unpatentable over Hochrainer in view of Remington's Pharmaceutical Sciences, Seventeenth Edition, 1985, pages 1443 and 1451.

The Examiner had cited the above-mentioned prior art references in previous Office Actions, including the Office Action dated August 27, 2007, to teach compositions

containing formoterol and steroid which are suitable for long term storage and direct administration, wherein the formoterol is in solution and the steroid is in suspension. The Examiner took the position that although none of the references cited expressly teach dilute formoterol-containing compositions suitable for long term storage and direct administration, one of skill in the art would have arrived at the present invention. Applicants responded to this point made by the Examiner on September 4, 2008, by showing the Examiner that: 1) the USPTO has consistently, and repeatedly found that such dilute aqueous formoterol-containing compositions as claimed in commonly assigned U.S. Patent Nos. 6,667,344 (the '344 patent), 6,814,953 (the '953 patent) and commonly assigned U.S. Patent Application Serial No. 10/887,785, (now U.S. Patent No. 7,348,362 (the '362 patent)) and U.S. Patent Application Nos. 11/688,429, 11/688,436, and 11/688,450 (now U.S. Patent Nos. 7,462,645 (the '645 patent), 7,465,756 (the '756 patent) and 7,473,710 (the '710 patent), respectively) are patentable over the same prior art cited by the Examiner in the present application; and 2) that the subject matter claimed herein is actually narrower than that already patented due to the requirement of the steroid in the formulation.

In the present Office Action dated October 28, 2008, the Examiner has taken the position that the teachings of the prior art render the claimed compositions obvious.

1. THE CLAIMS ARE NOT OBVIOUS OVER HOCHRAINER IN ALONE OR IN COMBINATION WITH ANY OF THE REFERENCES CITED BY THE EXAMINER

Applicants submit that the claimed subject matter of the present application is not merely a combination of known components. Rather, the present invention provides novel aspects that are neither taught nor suggested in the prior art. None of the prior art references teach compositions containing formoterol in a dilute solution and steroid anti-inflammatory agent in suspension, which is not only ready for direct administration, but also having long term storage stability. Additionally, none of the prior art references teach such compositions where the concentration of formoterol is about 5 μg/mL to about 200 μg/mL. Regardless of the reference relied upon by the Examiner, one would have to

dilute the prior art compositions in order to arrive at the formoterol concentration claimed herein. Such compositions are therefore not suitable for direct administration. Therefore, one would not arrive at the dilute ready to use compositions claimed herein by following the teachings of the prior art. Furthermore, none of the references teach or suggest that such dilute compositions would be stable for long term storage and direct administration.

Hochrainer teaches away from compositions as claimed in the present application. It is imperative that the Examiner take note of the fact that Hochrainer unequivocally requires the formoterol to be in a concentrated suspension in order to achieve long term storage. See Column 1, lines 55 et seq.;

> The active substance concentrate according to the invention refers to solutions or suspensions in which formoterol is dissolved or suspended in highly concentrated form in a pharmacologically suitable fluid and which are characterised in that the active substance, formoterol, can be stored therein for a period from several months possibly up to several years without any deterioration in the pharmaceutical quality.
>
> The term "active substance concentrate" denotes a solution or suspension of an active substance in which the active substance, formoterol, is present in highly concentrated form in a pharmacologically acceptable liquid as a solution or suspension. Suspensions are preferred as they have proved particularly stable on storage.
>
> The term "highly concentrated" means a concentration of the active substance which is usually too high to enable the corresponding solution or suspension to be used therapeutically for inhalation without being diluted. According to the invention the formoterol concentration in the active substance concentrate is between 10 mg/ml and 500 mg/ml. Preferably, the minimum concentration is at least 75 mg/ml. Preferred concentrations are between 100 mg/ml and 400 mg/ml, particularly between 250 mg/ml and 350 mg/ml.

This is contrary to the contrary to the claimed invention Applicants have shown that the opposite of what Hochrainer taught is possible, i.e. a dilute formoterol solution had long term stability and thus provides an advantage to those in the art administering the drug by avoiding the tedious dilution step. The 10 mg/ml lower limit of Hochrainer's range is still 20,000 times higher than the lower limit claimed in the present application.

A concentration of 20,000 times higher is not ready to use and Hochrainer specifically discloses diluting the same before use. In contrast, the long term storage suitable pharmaceutical compositions claimed herein are also at the same time, without dilution, suitable for direct administration. In fact, the claims expressly recite this novel aspect of the invention.

In Example 3, Hochrainer teaches that in "an aqueous solution (concentration not mentioned) with a pH of 5.0, formoterol breaks down to 10% at 40° C within only 3 months. In a comparable suspension, no breakdown of any kind can be observed even after 6 months' (sic) storage at 40° C" (col. 6, lines 56-59). Hochrainer thus unequivocally shows that formoterol solutions are not suitable for long term storage in solution and that only when formoterol is in suspension is it stable. Thus, the teachings of Hochrainer would not lead one of skill in the art to the claimed pharmaceutical compositions containing formoterol in dilute solution.

Hochrainer is also completely silent on whether a steroid could be included, let alone be combined with a dilute formoterol solution. The teachings of Hochrainer are completely different from the claimed compositions. The present application requires that the formoterol be in solution and that the steroidal anti-inflammatory is in suspension. In fact, Applicants note that the compositions containing formoterol in solution and steroidal anti-inflammatory in suspension as recited in claim 1 are surprisingly and unexpectedly stable, since typically formulations having one drug in solution and one drug in suspension are not stable. Applicants have found a successful means of combining dilute concentrations of formoterol and steroid. Thus, Hochrainer actually teaches away from compositions of the present application where the formoterol is in solution and the steroid is in suspension, and the claims of the present invention are not obvious. *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 727 (2007) (stating that "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious" (emphasis added)).

Applicants note that it is generally accepted by those of skill in the art that when dilute formulations are stable, it is not surprising that concentrated formulations are stable as well. However, the converse is not usually true. Therefore, just because Hochrainer discloses that concentrated formulations are stable, it cannot be said that dilute formulations would be stable. Therefore, the long term storage capabilities of the claimed ready to use, dilute compositions are surprising and unexpected over the teachings of Hochrainer. *Id.* (stating that "the fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that [the] design was not obvious to those of skill in the art").

The claimed limitation that the compositions are formulated for direct administration is urged not be seen as a mere optimization or packaging convenience. Instead, the claimed formulation is an advance over the prior art which repeatedly taught that formoterol had to be concentrated in order to have suitable long term stability. Hochrainer explicitly states that "[as] already explained, use of the active substance concentrate comprises converting it into a pharmaceutical preparation" (col. 4, lines 11-13). Thus, Hochrainer repeatedly teaches that there is a conversion step that must be taken in order to obtain a preparation suitable for administration from the preparation suitable for long term storage. Additionally, at Column 4, lines 2-4, Hochrainer states that "[it] is not necessary for the concentrate to correspond to the composition of the finished pharmaceutical preparation". Thus, not only does Hochrainer teach that there must be a dilution step when converting the concentrated pharmaceutical compositions to those suitable for administration, but there are other steps that must be taken to prepare the final pharmaceutical preparation. In fact, Hochrainer actually states that "the pH of the concentrate may differ substantially from the pH of the pharmaceutical preparation which is to be administered, if this ensures more stable storage of formoterol". Thus, the compositions suitable for long term storage as taught in Hochrainer require multiple steps in order to convert into a preparation suitable for administration, including dilution and pH adjustment. This is not the claimed compositions which are suitable for long term storage and are ready to administer without dilution or any other adjustments prior to administration.

Accordingly, the teachings of Hochrainer are not at all relevant to the direct administration qualities of the claimed formulation. The direct administration qualities of the claimed formulation allows the clinician to do away with an additional dilution and/or pH adjusting step. This also allows dosing calculation and/or dilution errors to be eliminated. Patients suffering from bronchoconstrictive disorders, such as chronic obstructive pulmonary disease often require immediate bronchodilation. Thus, the urgency of the situation may further lead to dilution and dosing mistakes during dilution and pH adjustment. Since Hochrainer requires additional steps to prepare a final pharmaceutical preparation, Hochrainer does not teach the claimed method of the present invention.

Hochrainer in view of Carling Does Not Render the Claimed Invention Obvious

Moreover, the combination of Hochrainer with Carling would not teach the claimed compositions. The shortcomings of Hochrainer are not cured by the secondary reference. The Examiner cited Carling as disclosing a formoterol concentration of 6-100 μg (col. 3, line 44). However, this is a dry powder concentration of formoterol, not formoterol in solution as claimed in the present application. There is no indication anywhere in Carling whether this concentration of formoterol would be appropriate for anything other than a metered dose inhaler or a dry powder inhaler. Accordingly, one of skill in the art would not look to the teachings of Carling to arrive at the formoterol concentration of the claimed invention. One does not arrive at the claimed invention by merely combining a reference which discloses a concentrated suspension with a MDI powder.

Additionally, each of the Examples and the disclosure pertaining to formulating the compositions of Carling are directed to dry powder formulations or dry powder which is later suspended in a liquid propellant mixture (see Examples 1-3 at col. 4, line 17-col. 5, line 14). In contrast, the compositions of the claimed invention are formulated in water that is propellant free, which is clearly not a dry powder or a liquid propellant formulation. In order to prepare the liquid propellant formulation of Carling, the dry powder must be suspended or dissolved. Carling, therefore, teaches a dilution step and is

not a ready to use composition like the compositions of the claimed invention. Respectfully, the combined teachings of Carling and Hochrainer would not lead one of skill in the art to the claimed invention.

Remaining Combinations Do Not Render the Claimed Invention Obvious

The Examiner cited PDR, Hardman, Leckie and Remington's Pharmaceutical Services to teach the elements missing from the combination of Hochrainer and Carling. Applicants respectfully submit that these secondary references do not cure the deficiencies of Hochrainer and Carling, and thus, would not lead one of skill in the art to the present invention. The secondary references do not disclose compositions with formoterol in solution and steroid in suspension in propellant-free water that are suitable for long-term storage and direct administration without dilution. Thus, the secondary references in combination with Hochrainer and Carling neither teach nor suggest the pharmaceutical compositions of the present invention.

Since none of the references cited by the Examiner in combination with Hochrainer teach or suggest dilute aqueous solutions containing a combination of formoterol and steroid, where the formoterol is in solution and the steroid is in suspension, in propellant-free water, and where the dilute aqueous solutions are suitable for both long term storage and direct administration, it is respectfully submitted that the combination of the references cited by the Examiner would not have led one of ordinary skill in the art to the claimed invention. Thus, applicants submit that the claims presented herein are patentable over the Examiner's rejections and that this application is in condition for allowance and such action is respectfully and earnestly requested.

2. THE USPTO HAS REPEATEDLY FOUND THAT DILUTE AQUEOUS FORMULATIONS WERE PATENTABLE OVER THE PRIOR ART CITED BY THE EXAMINER

Applicants noted in the previous response of September 4, 2008 that the USPTO has consistently and repeatedly found that the dilute aqueous formoterol-containing compositions as claimed in commonly assigned patents, namely, the '344 patent, the '953

patent, the '362 patent, the '645 patent, the '756 patent and the '710 patent are patentable over the same prior art cited by the Examiner in the present application. Thus, during the prosecution of the aforementioned commonly assigned six patents, the USPTO had found that the claimed subject matter was patentable over Hochrainer, Carling, PDR, Hardman, Leckie and Remington's.

Applicants also note that the '344 patent, the '953 patent, the '362 patent and the '756 patent were cited in double patenting rejections discussed *infra* made by the Examiner in the present Office Action. This application is entitled to an effective filing date of April 17, 2001 (provisional application No. 60/284,607), which is the same date as or an even earlier date than the patents cited by the Examiner in these double patenting rejections. The conclusion is that the present application, entitled to the same or earlier priority date as the patents cited in the double patenting rejections, is clearly also patentable over the same Hochrainer-based combinations.

A difference between the present application and the aforementioned commonly assigned patents is that the present application includes subject matter directed to compositions containing formoterol and a steroidal anti-inflammatory agent suitable for long term storage and direct administration. Therefore, the scope of the claims in the present application is, in fact, narrower than the scope of the claims which issued in the aforementioned patents. Since broader claims were found patentable over the same prior art cited by the Examiner, the narrower claims currently pending in the present application should also be deemed patentable. Moreover, since the USPTO has repeatedly and consistently found that the prior art references neither teach nor suggest the formoterol-containing compositions of the aforementioned patents, the references undoubtedly neither teach nor suggest the formoterol and steroid-containing compositions claimed in the present application.

Moreover, in the present Office Action, the Examiner took the position that the claimed subject matter is not patentably distinct from the aforementioned commonly assigned patents and made double patenting rejections. Thus, the Examiner agrees that

the dilute aqueous formoterol-containing portion of the compositions claimed in the '344 patent, the '953 patent, the '362 patent and the '756 patent are the same as that claimed in the present application. Since the Examiner agrees that the claimed subject matter in the present application is not patentably distinct from the commonly assigned patent claims, the claims presented herein must also define patentable subject matter over the same references. Note also the '344 patent which claims long term storage formoterol compositions corresponding to the formoterol included in the combination claimed herein. In order to advance prosecution of the present application, Applicants submit herewith Terminal Disclaimers in view of commonly assigned U.S. Patent Nos. 7,465,756, 7,348,362, 6,667,344 and 6,814,953.

D. DOUBLE PATENTING

The Examiner has made the following four double patenting rejections:

(1) Claims 1, 3-21, 23-38, 40-64, 69-74, 78-83, 87-89, 93 and 99-146 have been rejected on the grounds of non-statutory obviousness-type double patenting over U.S. Patent Application No. 11/688,436 7 (now U.S. Patent No. 7,465,756);

(2) Claims 1, 3-21, 23-38, 40-64, 69-74, 78-83, 87-89, 93, 99-128 and 129-146 have been rejected on the grounds of non-statutory obviousness-type double patenting over U.S. Patent No. 7,348,362;

(3) Claims 1, 3-21, 23-38, 40-64, 69-74, 78-83, 87-89, 93 and 99-146 have been rejected on the grounds of non-statutory obviousness-type double patenting over U.S. Patent No. 6,667,344; and

(4) Claims 1, 3-21, 23-38, 40-64, 69-74, 78-83, 87-89, 93 and 99-146 have been rejected on the grounds of non-statutory obviousness-type double patenting over U.S. Patent No. 6,814,953.

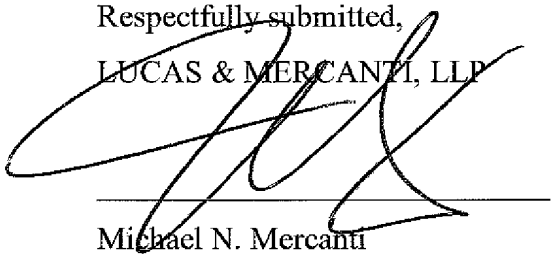
This response is being submitted with Terminal Disclaimers in view of commonly assigned U.S. Patent Nos. 7,465,756, 7,348,362, 6,667,344 and 6,814,953 along with the fees required therefor.

E. FEES

A two-month extension of time is hereby requested and the extension of time fee is hereby paid along with the online filing. No further fees are believed to be due. If it is determined that any further fees are due or any overpayment has been made, the Assistant Commissioner is hereby authorized to debit or credit such sum to Deposit Account No. 02-2275. Pursuant to 37 C.F.R. 1.136(a)(3), please treat this and any concurrent or future reply in this application that requires a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. The fee associated therewith is to be charged to Deposit Account No. 02-2275.

Respectfully submitted,

LUCAS & MERCANTI, LLP



Michael N. Mercanti
Registration No. 33,966

LUCAS & MERCANTI, LLP
475 Park Avenue South
New York, New York 10016
Phone: 212-661-8000
Fax: 212-661-8002